Predictive value for weakness and 1-year mortality of screening electrophysiology tests in the ICU

Running title: Reduced CMAP independently predicts 1-y mortality

Greet Hermans [1,2]* Helena Van Mechelen [1*], Frans Bruyninckx [3], Tine Vanhullebusch [1], Beatrix Clerckx [4], Philippe Meersseman [2], Yves Debaveye [1,4], Michael P. Casaer [1,4], Alexander Wilmer [2], Pieter J. Wouters [1,4], Ilse Vanhorebeek [1], Rik Gosselink [5], Greet Van den Berghe [1,4]

[1]Laboratory of Intensive Care Medicine, Division of Cellular and Molecular Medicine, KU Leuven, Belgium; [2]Medical Intensive Care Unit, Department of General Internal Medicine, University Hospitals Leuven, Belgium; [3]Department of Physical Medicine and Rehabilitation, University Hospitals Leuven, Belgium; [4]Department of Intensive Care Medicine, University Hospitals Leuven; [5]Department of Rehabilitation Sciences, KU Leuven, Belgium.

*Equally contributed

Correspondence to: Greet Hermans, MD, PhD, Medical Intensive Care Unit, Department of General Internal Medicine, University Hospitals Leuven and Laboratory of Intensive Care Medicine, Division of Cellular and Molecular Medicine, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium Tel: +32-16-344275, Fax: +32-16-344230, Email: Greet.Hermans@uzleuven.be

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Abstract

Purpose: Muscle weakness in long-stay ICU patients contributes to 1-year mortality. Whether electrophysiological screening is an alternative diagnostic tool also in unconscious/uncooperative patients remains unknown. We aimed to determine the diagnostic properties of abnormal compound muscle action potential (CMAP), sensory nerve action potential (SNAP) and spontaneous electrical activity (SEA) for MRC-defined weakness and their predictive value for 1-year mortality.

Methods: Data were prospectively collected during the EPaNIC trial (ClinicalTrials.gov:NCT00512122). First, sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of abnormal CMAP, SNAP and SEA for weakness were determined. Subsequently, association between 1-year mortality and abnormal findings on electrophysiological screening was assessed by univariate and multivariate analyses correcting for weakness and other risk factors and the prediction model involved only a development phase.

Results: 730 patients were electrophysiologically screened of whom 432 were tested for weakness. On day 8, normal CMAP excluded weakness with a high NPV (80.5%). By day 15, abnormal SNAP and the presence of SEA revealed a high PPV (91.7% and 80.0%, respectively). Only a reduced CMAP on day 8 was associated with higher 1-y mortality [35.6% versus 15.2% ($p<0.001$)]. This association remained significant after correction for weakness and other risk factors [OR:2.463 (95%CI:1.113-5.452), p=0.026]. Also among conscious/cooperative patients without weakness, reduced CMAP was independently associated with a higher likelihood of death occurring during 1 year [HR:2.818 (95%CI:1.074-7.391), p=0.035].

Conclusions: The diagnostic properties of electrophysiological screening vary over time. Abnormal CMAP documented early during critical illness carries information about longer-term outcome, which should be further investigated mechanistically.

Key words: electrophysiology, intensive care, muscle weakness, mortality

INTRODUCTION

Critically ill patients often develop weakness due to functional and structural alterations in nerves, muscles or both. The diagnosis of ICU-acquired neuromuscular disorders is primarily based on clinical strength assessment, using the Medical Research Council (MRC) sum-score [1, 2]. This score quantifies strength in 6 muscle groups bilaterally, with a summed score <48 indicating clinically relevant weakness [2, 3]. About 50% of patients with sepsis, multiple organ failure or requiring prolonged mechanical ventilation suffer from weakness [4]. Association studies suggested that weakness is a burden in the acute [3, 5-8] and chronic phase of critical illness [9, 10]. Recently, we showed that weakness present after one week of critical illness contributes to ICU and hospital morbidity, increased hospitalization costs and 1-year mortality [8].

The MRC-based diagnosis requires patients to be awake and cooperative. Between 22% and 53% of patients [3, 6, 7, 11] therefore remain clinically not assessable in the ICU. Electrophysiological screening including the quantification of compound muscle action potentials (CMAP), sensory nerve action potentials (SNAP) and the presence of spontaneous electrical activity (SEA), here could serve as an alternative diagnostic tool (Figure 1) [12-14]. However, diagnostic properties of abnormal CMAP, SNAP and SEA for weakness in the ICU are not well characterized. Additionally, electrophysiological features could reflect other pathophysiological alterations, evoked by critical illness or pre-existing, that could be important for survival, related to or independent of weakness [15].

In this large prospective study, we determined the diagnostic properties of abnormal CMAP, SNAP and SEA for MRC-defined weakness after one and two weeks of critical illness. We hypothesized that abnormal CMAP, SNAP or SEA upon electrophysiological screening 1 week after ICU admission relate to longer-term mortality, and assessed whether these associations depend on the presence of weakness as well as on baseline characteristics and exposure to ICU-related risk factors prior to electrophysiological screening. This is a development-only phase of a prognostic prediction model, aimed to specifically address the independent role of electrophysiological characteristics for 1-year mortality [16].

METHODS

The trial protocol and consent forms were approved by the institutional ethical review board (ML4190).

Patients

This study is a preplanned sub-analysis of the EPaNIC trial [17], which included 4640 patients and examined early versus late administration of parenteral nutrition to supplement insufficient enteral nutrition in critically ill patients [18]. Identification of risk factors for 1-year mortality (see statistical analyses) was done in the total EPaNIC population.

From October 2008 onwards, patients requiring intensive care for ≥8 days, further referred to as long-stay patients, received systematic electrophysiological screening once weekly, until ICU discharge or death. We *a priori* selected these patients for screening because of their increased risk of developing weakness. The first evaluation was planned on day 8 (±1 day for feasibility reasons). As it is unknown to what extent ICU patients with favorable clinical evolution have electrophysiological abnormalities, we also included a random sample of short-stay patients discharged alive from the ICU but still in hospital at day 8. The random sample was computer-generated in a 1/10 ratio and stratified according to diagnostic admission categories. These patients received electrophysiological screening on day 8±1 on the ward (Figure 2). From December 2008 onwards, MRC sum-score was systematically assessed 3 times weekly in awake long-stay patients [8, 11]. Also here, a random sample of short-stay patients was included. Patients with neuromuscular disorders identified prior to ICU admission, or in whom this was the reason for ICU admission were excluded (see online supplement). Other exclusion criteria were patient refusal, unavailability of patient/assessor at planned examination, and decrement on repetitive nerve stimulation, indicating neuromuscular blocking.

Electrophysiological tests

For nerve conduction studies, 1 standard motor and 1 sensory nerve were evaluated in both upper and lower limbs unilaterally. We defined reduced CMAP and SNAP when below the lower limit of normal in both nerves of both limbs [19]. Needle electromyography in rest was performed unilaterally in 1 standard proximal and 1 distal muscle in both upper and lower limbs. Abundant SEA was defined as the presence of sustained fibrillation potentials and/or positive sharp waves in at least 2 muscles of at least 2 limbs. (see online supplement)

MRC sum-score

The MRC sum-score was evaluated as described [11, 20] and assessed by physiotherapists blinded for electrophysiological data (see online supplement).

Statistical analyses

Data were analyzed using IBM SPSS-20 (SPSS Inc). Baseline and outcome variables are presented as median and interquartile range or number and proportions. Results were compared using Mann-Whitney U test, chi-square test, logistic regression analysis and Cox-proportional-hazard analysis. Differences were considered significant when 2-sided p-values ≤ 0.05.

The 2 primary outcomes were (i) sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) of abnormal CMAP, SNAP and SEA for weakness (MRC sum-score<48) and (ii) the predictive value for 1-year mortality of abnormal electrophysiology results, documented at first evaluation. Data on index and reference test are reported according to the Standards for Reporting of Diagnostic Accuracy [21].

First, incidence of abnormal CMAP, SNAP and SEA was determined in the total screened population and in the 432 cooperative patients tested for weakness. In the latter subgroup, sensitivity, specificity PPV and NPV of abnormal CMAP, SNAP and SEA for weakness were analyzed at the first and second electrophysiological

evaluation. Second, association between 1-year mortality and abnormal findings on the first electrophysiological screening was assessed by univariate analysis and, when significant, multivariate analyses were performed correcting for weakness and other risk factors. Baseline risk factors for 1-year mortality, risk factors to which patients were exposed in ICU prior to first electrophysiological assessment (including new infection, treatment with neuromuscular blocking agents, duration of corticosteroid administration and duration of mechanical ventilation), and the site of electrophysiogical testing, were identified by univariate regression analysis ($p<0.2$) (Table E2).

Multivariate logistic regression analysis of the screened population was performed in 2 steps, first assessing the independent predictive value of any abnormal electrophysiological result corrected for weakness, and second further correcting for other pre-existing and ICU-acquired risk factors. Risk factors were assigned to the final model with use of a backward method (likelihood ratio, probability for enter 0.1, removal 0.2). Model performance is reported with the Hosmer-Lemeshow test, c-statistic and visualized by the ROC curve. To exclude excessive correlation that might prevent obtaining useful information we checked correlation coefficients [22] and performed a forward (likelihood ratio) multiple regression analysis [23]. As MRC-sum <48 remains an arbitrary limit, we planned post-hoc determination of its optimal cut-off for 1-year mortality and used this to repeat the analysis.

To further examine whether weakness and electrophysiology hold different information for long-term outcome, patients were categorized into 4 groups according to MRC and electrophysiology. Cox-proportional-hazard analysis for 1-year survival was performed for these groups, corrected for the covariates identified in the multivariate logistic regression model. The time variable entered was calculated from the time of MRC evaluation or electrophysiological testing, which ever came last, up to 1 year after ICU admission.

RESULTS

Patient characteristics

Electrophysiological screening was performed in 730 patients (online Figure E1) on median day 8 (IQR 8-8). This comprised 88 short-stay and 642 long-stay patients. Baseline and outcome variables are depicted in Table 1&E3.

In 432 patients, MRC sum-score was also obtained. In this subset, electrophysiological testing was performed on day 8 (IQR 8-9) and MRC sum-score on day 10 (IQR 8-14). The delay from electrophysiological testing up to the clinical evaluation was 2 days (IQR 0-6). This subgroup clearly differed from the subgroup that could not be clinically tested (Table 1).

Diagnostic properties of electrophysiological screening for clinical weakness

In the total population of 730 patients, abnormal CMAPs, SNAPs and SEA occurred in respectively 75.5%, 11.1% and 20.4% of patients (Table 2). Inevitably, analyses of diagnostic properties of these features was performed in the 432 patients who received both MRC and electrophysiology assessment on day 8. The incidence of abnormal CMAP and SEA was somewhat lower in the cooperative subgroup with MRC sum-score (Table 2).

Reduced CMAP on day 8 had high sensitivity (88.6%), high NPV (80.5%) but low specificity (41.0%) for weakness at first examination (Table 2). Reduced SNAP had a low incidence and very low sensitivity for detecting weakness (13.6%), although it was highly specific (93.5%). Abnormal SEA exhibited a similar pattern with specificity of 89.3% but only 20.7% sensitivity. No single or combined (data not shown) electrophysiological feature exhibited high sensitivity *and* high specificity for detecting weakness on day 8.

When also taking the second electrophysiological screening on day 15 (IQR: 15-15) into account, the incidence of electrophysiological abnormalities increased. Abnormal SNAP or the presence of SEA then revealed a very high PPV (91.7% and 80.0%, respectively), whereas the NPV of abnormal CMAP decreased (54.5%). Also on

day 15, combination of electrophysiological features did not substantially improve diagnostic properties (data not shown).

Predictive value of electrophysiological screening for 1-year mortality

In univariate analysis, only CMAP on day 8 was significantly associated with 1-year mortality (Table E4). Patients with abnormal CMAP had higher 1-year mortality than patients with normal CMAP (35.6% versus 15.2%, p<0.001). This difference was present among patients with (26.2% versus 8.0%, p<0.001) and without MRC (48.2% versus 29.3%, p=0.010) (Table E5). Also other outcomes were worse for patients with abnormal as compared to normal CMAP (Table E5).

In multivariate analysis, adding weakness to the model revealed that both abnormal CMAP and weakness were independently associated with 1-year mortality (Table 3). Further adding the other risk factors, including baseline risk factors among which co-morbidities, ICU exposures and site of electrophysiological assessment did not alter this result (final OR for abnormal CMAP: 2.463, 95%CI: 1.113-5.452, p=0.026 and for weakness: 1.955, 95% CI: 1.116-3.425, p=0.019). None of the risk factors to which patients were exposed in ICU prior to electrophysiological screening remained associated with 1-year mortality in the multivariate model (Table 3) with a Hosmer-Lemeshow test p=0.147 and c-statistic = 0.779 (95%CI: 0.730-0.829) (Figure E2). The forward regression model retained the same factors as the backward model. Sensitivity analyses, using the optimal discriminating MRC sum-score cut-off for 1-year mortality of 53 yielded similar results (data not shown).

Cox-proportional hazard analysis of survival within the first year following ICU admission further confirmed that patients with reduced CMAP but no weakness had a higher likelihood for earlier death (HR: 2.818, 95% CI: 1.074-7.391, p=0.035) as compared to patients with normal CMAP and no weakness. The same was true for patients with both weakness and abnormal CMAP (HR: 4.773, 95% CI: 1.882-12.106 p=0.001) (Figure 3).

DISCUSSION

We showed that reduced CMAP on screening electrophysiological testing 8 days after ICU admission in a heterogeneous population of critically ill patients, is highly sensitive but not specific for weakness, with a high NPV for weakness. This suggests that early abnormal CMAP reflects neuromuscular alterations that are at least in part distinct from weakness. However, when repeated on day 15 in ICU, any abnormal SNAP or the presence of SEA revealed a high PPV for weakness. The observation that abnormal CMAP on day 8 remained significantly associated with 1-year mortality in multivariate analysis, independent of weakness and other risk factors, further supports that these pathophysiological alterations are important for longer-term outcome.

Accuracy of simplified electrophysiological testing to detect critical illness polyneuropathy (CIP) or myopathy (CIM) as defined by extensive electrophysiological testing was evaluated previously. Latronico et al. found that peroneal nerve CMAP had high sensitivity [19, 24] and specificity [24] for such a diagnosis based on full electrophysiological testing. Moss et al. found that combining peroneal and sural amplitudes further increased accuracy [15]. The current study differs from previous investigations by assessing diagnostic properties of simplified electrophysiological screening for weakness and its predictive value for longer-term outcome.

We found that predictive properties of electrophysiological screening for weakness depend on the time after onset of critical illness when tests were performed. Normal CMAP one week after onset of critical illness allowed excluding weakness with a high NPV, but this property was not maintained later on. Our findings on early CMAP results correspond with other reports. Weber-Carstens [25] found in 44 patients a sensitivity of 92% and specificity of 44%. Similarly, Wieske et al. found in 35 patients that both ulnar and peroneal CMAP reduction had 100% sensitivity but respectively 0% and 31% specificity to detect weakness [26]. This concurs with a higher incidence of electrophysiological abnormalities as compared to weakness in critical illness [27, 28]. The early high incidence of abnormal CMAP, presumed to reflect both myopathies and neuropathies, suggests that this electrophysiological finding captures more than the problem of weakness.

In contrast, abnormal SNAP documented later during critical illness, which may indicated neuropathy, allowed diagnosing weakness with a high PPV, which has not been reported earlier. This high PPV of abnormal SNAP is in line with Lefaucher et al. [29] who reported reduced SNAPs in 17/30 patients diagnosed with weakness about

two weeks after onset of illness. Zifko et al. [30] found reduced SNAPs in 71% of 62 patients with weakness 40 days after ICU admission. The higher incidence of abnormal SNAP in both studies as compared with our study is explained by the selection of weak patients, referred for electrophysiology rather than systematically screened.

We found a high PPV of SEA for weakness later during critical illness. This is in line with Weber-Carstens et al [25], who reported a specificity of 93% and sensitivity of 48% for detection of weakness by SEA using repetitive weekly screening. SEA, which may occur both in neuropathy and myopathy [13], develops later than abnormal CMAP [27, 31, 32] and incidence increases with duration of ICU stay [33, 34]. In two RCTs, tight glucose control reduced the incidence of SEA approximately by half [33, 34]. We here document a similar incidence as in the tight glucose control arm of these studies, possibly explained by the routine implementation of tight glucose control.

To the best of our knowledge, this study is the first to demonstrate that abnormal CMAP 8 days after ICU admission was independently associated with 1-year mortality. This was true independent of weakness. Earlier studies reported that electrophysiological signs of CIP and CIM were related with poor short-term prognosis, including prolonged ICU and hospital stay, prolonged mechanical ventilation, prolonged rehabilitation and increased hospital mortality [15, 35-40] which we here confirmed. Others suggested that this merely reflected illness severity [19, 30]. One study of 50 patients also examined the association of electrophysiological abnormalities with 1-year mortality but did not find a significant effect, possibly related to lack of power [38]. Our findings that abnormal CMAP was independently associated with 1-year mortality, an outcome clearly exceeding the index hospitalization, are therefore novel. This opens perspectives for identification of patients who might benefit from future interventions to improve outcome. As such, electrophysiology appears to hold information required for screening tools for ICU-acquired weakness, as recently stated by the ATS [2].

The reason why abnormal CMAP was related to 1-year mortality, independent of other risk factors, remains speculative as we did not prospectively evaluate causes of death. The most obvious explanation that reduced CMAP predicts weakness, which by itself contributes to 1-year mortality, was invalidated as the association between reduced CMAP and 1-year mortality was independent of weakness. This suggests that CMAP reduction and weakness possibly identify different, though overlapping, phenotypes of neuromuscular involvement, as recently hypothesized [14]. Alternatively, this could point to subclinical weakness not captured by the MRC

sum-score. CMAP reduction, reflecting derangement of excitable nerve/muscle tissue, can be an early biological sign, according to the theory of bioenergetic failure [19, 41]. Finally, reduced CMAPs could carry information about pathophysiological alterations determining longer-term outcome, not necessarily related to weakness. This should be further investigated mechanistically.

This study has some limitations and strengths. First, we only performed screening electrophysiological tests as we aimed to examine a large ICU population. Therefore, sophisticated tests such as direct muscle stimulation, which could have differentiated between neuropathy and myopathy [27, 29, 42, 43], have both high sensitivity and specificity for weakness and may precede the diagnosis of weakness by a week [25] were not feasible. For similar reasons, also follow-up testing including voluntary muscle contraction was not systematically performed. Hence, we cannot differentiate between the role of neuropathy and myopathy in the association with 1-year mortality. We also a priori chose to collect amplitudes as dichotomous data, analogously to other studies evaluating electrophysiology as a screening tool [19, 24]. In addition, we used alternative nerves if the standard nerves were not evaluable. As reference values depend on the nerves evaluated, dichotomization allowed us to cope with this issue. We cannot exclude that use of absolute values would have provided additional information. All electrophysiological data were protocolized by a single electrophysiologist, which may limit generalizability. The case-mix was mainly surgical ICU patients with 27.8% cardiac surgery patients. Diagnostic properties may depend on case mix and severity of weakness. Also, we cannot exclude bias from selection of patients who were screened as compared to those in whom patient or assessor was not available. Finally, we corrected as much as possible for premorbid risk factors and severity of illness. We cannot exclude that other unknown conditions brought about a reduced CMAP and contributed to the higher risk of 1-year mortality, as premorbid functional assessment or baseline nerve conduction studies were not available [15]. The strengths of this study are the large sample size, its prospective design, the systematic and repeated screening electrophysiology and concomitant MRC sum-score measurements. There is no gold standard for diagnosing ICU-related neuromuscular complications but, as a more reliable test has not yet emerged, MRC-sum <48 was regarded as the reference standard by the ATS [2].

In conclusion, early during critical illness, CMAP had a high NPV for the diagnosis of weakness whereas later, SNAP and SEA revealed a high PPV. One week after onset of critical illness, abnormal CMAP was the only electrophysiological characteristic associated with 1-year mortality, independent of weakness and other risk

factors. This suggests that CMAP may carry information about longer-term outcome and could be useful to identify patients for future interventional studies aiming to improve outcomes.

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Figure legends

Figure 1: Screening electrophysiological tests

CMAP: compound muscle action potential; SNAP: sensory nerve action potential; SEA: spontaneous electrical activity

Figure 2: Patient flow chart

ICU: intensive care unit; NMD: neuromuscular disease; MRC: Medical Research Council

Figure 3: Cox regression estimates for survival in the first year after ICU admission.

The survival curve visually displays the model predicted survival time for the 'average' patient (this means with other covariates fixed at their average values) according to the results of CMAP at day 8 and presence or absence of weakness at first MRC-sum score measured from day 8 onwards. Covariates entered in the model are those that were retained by the multivariate logistic regression model for 1 year survival and included age, BMI<25 or >40, malignancy and sepsis upon admission. The time variable entered in the model was calculated from the time of electrophysiological testing or MRC sum-score, which ever came last, up to 1 year after ICU admission.

Table 1. Baseline characteristics and outcomes for patients receiving electrophysiological screening

	Total population N=730	With MRC N=432	Without MRC N=298	P-value
Baseline characteristics				
Age, years, median (IQR)	64 (53-74)	64 (53-73)	64 (54-75)	0.233
APACHE II score, median (IQR)	32 (24-38)	33 (23-38)	32 (26-39)	0.242
Sex, male sex, N (%)	462 (63.2)	253 (58.6)	209 (70.1)	**0.001**
BMI<25 or>40, N (%)	371 (50.8)	229 (53.0)	142 (47.7)	0.155
NRS <5, N (%)	506 (69.3)	298 (69.0)	208 (69.8)	0.814
Diabetes mellitus, N (%)	127 (17.4)	69 (16.0)	58 (19.5)	0.221
Malignancy, N (%)	183 (25.1)	113 (26.2)	70 (23.5)	0.414
Pre-admission dialysis, N (%)	12 (1.6)	6 (1.4)	6 (2.0)	0.514
Sepsis, N (%)	355 (48.6)	207 (47.9)	148 (49.7)	0.642
Admission category				**0.002**
Cardiac surgery, N (%)	203 (27.8)	134 (31.0)	69 (23.2)	
Elective surgery, N (%)	29 (4.0)	22 (5.1)	7 (2.3)	
Emergent surgery, N (%)	348 (47.7)	204 (47.2)	144 (48.3)	
MICU, N (%)	150 (20.5)	72 (16.7)	78 (26.2)	
Randomization to late PN, N (%)	363 (49.7)	220 (50.9)	143 (48.0)	0.435
Outcomes				
Duration MV, days, median (IQR)	9 (5-18)	8 (4-17)	11 (6-18)	**0.002**
Time to live weaning from MV, days, median (IQR)	10 (5-24)	8 (4-18)	13 (6-283)	**<0.001**
ICU length of stay, days, median (IQR)	14 (10-23)	14 (9-26)	14 (10-22)	0.918
Time to live ICU discharge, days, median (IQR)	15 (10-33)	14 (9-26)	18 (10-283)	**<0.001**
ICU mortality (N, %)	103 (14.1)	21 (4.9)	82 (27.5)	**<0.001**
Hospital length of stay, days, median (IQR)[a]	33 (21-55)	35 (21-58)	31 (20-49)	**0.016**
Time to live hospital discharge, days, median (IQR)	47 (26-207)	39 (24-84)	76 (31-380)	**<0.001**
Hospital mortality (N, %)	176 (24.1)	54 (12.5)	122 (40.9)	**<0.001**
1y mortality (N, %)[b]	230 (31.6)	95 (22.0)	135 (45.5)	**<0.001**

Abbreviations: MRC: Medical Research Council; IQR: interquartile range; APACHE II: acute physiology and chronic health evaluation; BMI: body mass index; NRS: nutritional risk score; MICU: medical ICU; ICU: intensive care unit; MV: mechanical ventilation; PN: parenteral nutrition

[a]Hospital stay was shorter, explained by higher hospital mortality and longer time to live hospital discharge

[b]1y-survival status is unknown for 2 foreigners

Table 2. Incidence of electrophysiological abnormalities on the first and second evaluation and their predictive value for ICUAW

	Incidence in total population	Incidence in patients with MRC sum-score	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)
First electrophysiological screening	**N=730**	**N= 432**				
CMAP reduced or absent	527/698 (75.5%)	302/415 (72.8%)	88.6% (83.0-92.6)	41.0% (34.5-47.8)	56.6% (50.8-62.3)	80.5% (71.8-87.1)
SNAP reduced or absent	71/638 (11.1%)	37/384 (9.6%)	13.6% (9.0-19.9)	93.5% (89.1-96.3)	62.2% (44.8-77.1)	57.9% (52.5-63.1)
Abnormal SEA	146/716 (20.4%)	65/423 (15.4%)	20.7% (15.4-27.2)	89.3% (84.4-92.9)	63.1% (50.2-74.4)	56.1% (50.8-61.3)
Second electrophysiological screening	**N=327**	**N=195**				
CMAP reduced or absent	284/320 (88.8%)	167/189 (88.4%)	92.3% (85.9-96.0)	20.3% (11.4-33.2)	71.9% (64.3-78.4)	54.5% (32.6-74.9)
SNAP reduced or absent	45/290 (15.5%)	24/172 (14.0%)	18.5% (12.2-26.9)	96.2% (85.9-99.3)	91.7% (71.5-98.5)	34.5% (27.0-42.8)
Abnormal SEA	129/324 (39.8%)	55/193 (28.5%)	33.1% (25.3-41.8)	81.7% (69.1-90.1)	80.0% (66.6-89.1)	35.5% (27.7-44.2)

Abbreviations: MRC: Medical Research Council; CMAP: compound muscle action potential; SNAP: sensory nerve action potential; SEA: spontaneous electrical activity
Different denominators are due to technical issues precluding evaluation of certain electrophysiological tests in some patients

Table 3. Multivariate logistic regression analysis for the risk of death 1 year after ICU admission

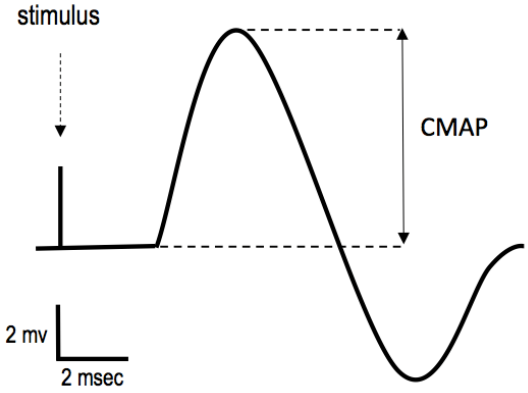
	OR	p value
A. Uncorrected		
Abnormal CMAP	3.076 (1.954-4.844)	**<0.001**
B. Corrected for weakness		
Abnormal CMAP	3.115 (1.466-6.616)	**0.003**
MRC sum-score <48	2.128 (1.274-3.556)	**0.004**
C. Corrected for weakness, baseline risk factors[a], ICU risk factors prior to electrophysiological testing[b] and site of testing		
Abnormal CMAP	2.463 (1.113-5.452)	**0.026**
MRC sum-score <48	1.955 (1.116-3.425)	**0.019**
Age	1.045 (1.022-1.069)	**<0.001**
BMI <25 or >40	1.800 (1.045-3.099)	**0.034**
Malignancy	2.892 (1.669-5.011)	**<0.001**
Sepsis on admission	1.849 (1.056-3.237)	**0.032**
NRS≥5	1.508 (0.870-2.614)	0.143

Abbreviations: OR: odds ratio; CMAP: compound muscle action potential; MRC: Medical Research Council; BMI: Body Mass Index; NRS: nutritional risk score

[a]baseline risk factors included are: age, BMI, NRS, APACHE II, diagnostic categories, diabetes, malignancy, pre-admission dialysis, sepsis on admission

[b]ICU risk factors prior to electrophysiological screening included are: new infections, neuromuscular blocking agents, corticosteroids and duration of mechanical ventilation up to day 8 of ICU admission

Figure 1

<table>
<tr>
<td rowspan="2">Nerve conduction studies</td>
<td>Motor nerve conduction studies:
A peripheral nerve is stimulated and the evoked compound muscle action potential (CMAP) is recorded with use of surface electrodes overlying a muscle supplied by that nerve. CMAP is reduced in neuropathy and myopathy.
 
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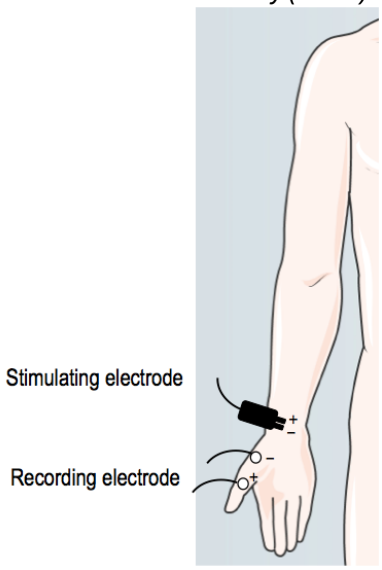
<td>Median nerve motor study (CMAP)
 
</td>
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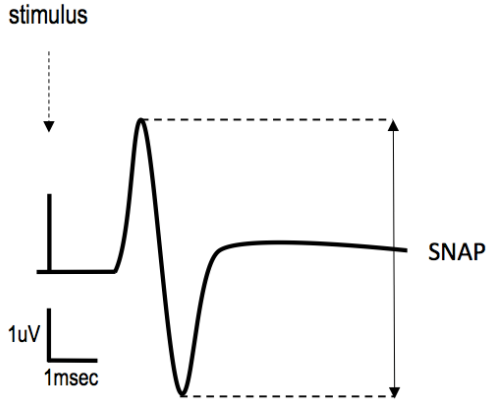
<tr>
<td>Sensory nerve conduction studies:
A peripheral nerve is stimulated and the evoked sensory nerve action potential (SNAP) is obtained with surface electrodes from a purely sensory distal part of the stimulated nerve. SNAP is reduced in neuropathy. As absolute values of SNAPs are much smaller than absolute values of CMAPs, SNAPs are more affected by limb edema.
 
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 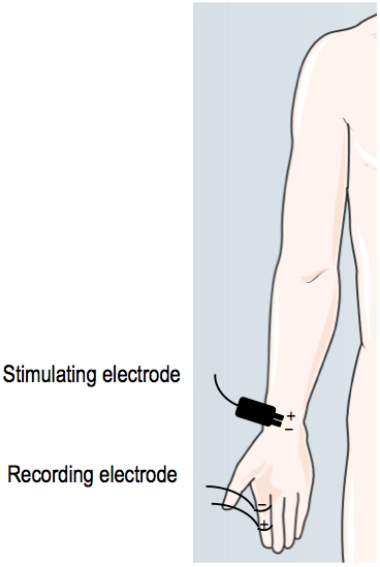
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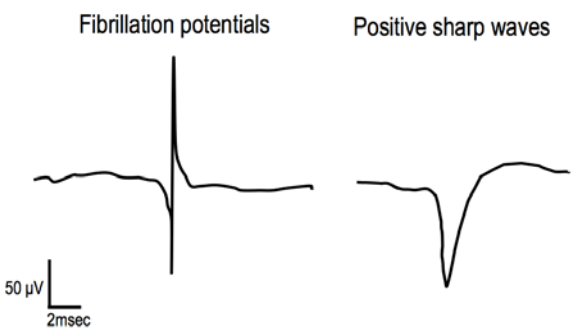
<td>Electromyography</td>
<td>Electrical muscle activitiy in rest:
This is registered with use of a concentric needle. Abnormal spontaneous electrical activity (SEA) occurs as fibrillation potentials and/or positive sharp waves and may be present in case of denervation or muscle necrosis.
 
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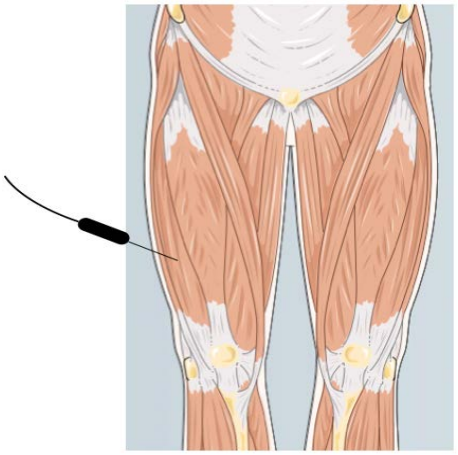
<td>Electromyography of the vastus lateralis of the quadriceps muscle
  </td>
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Figure 2

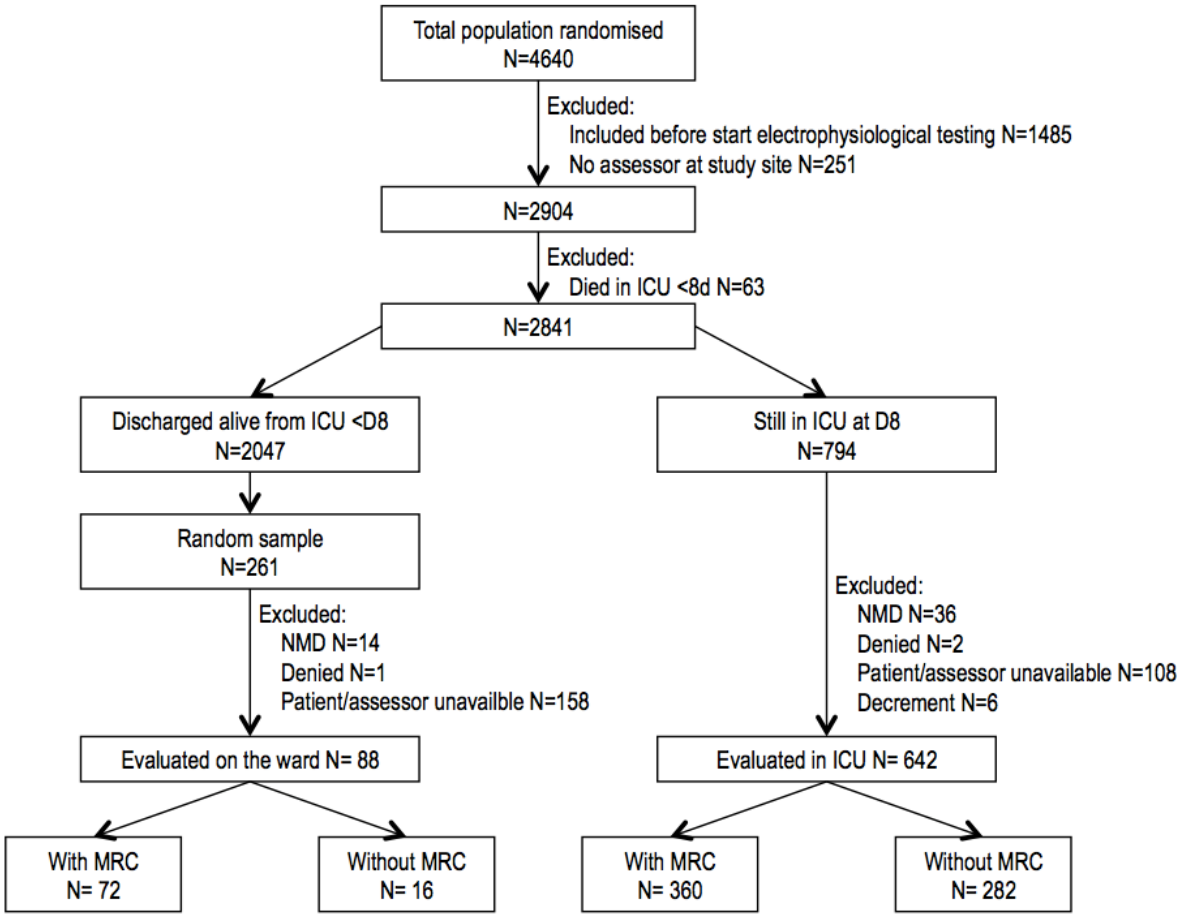
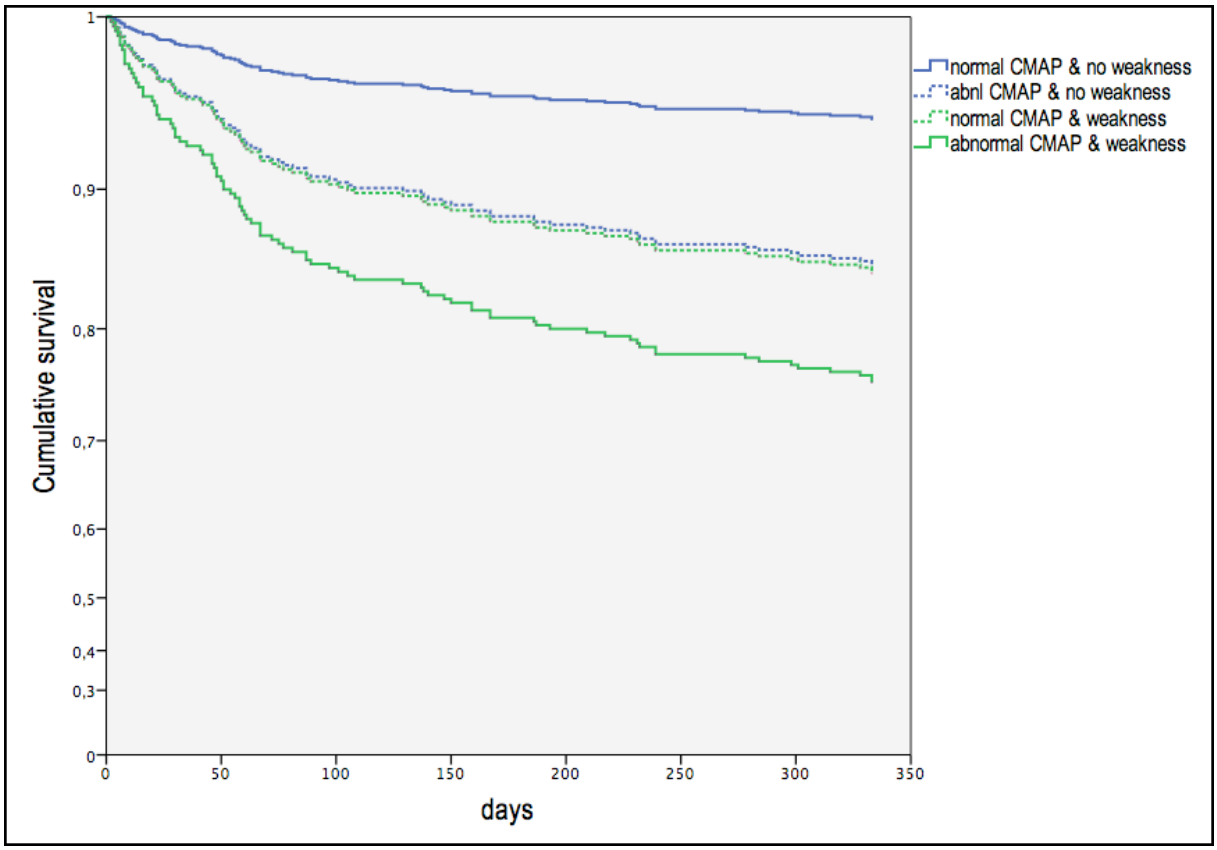

Total population randomised
N=4640
Excluded:
Included before start electrophysiological testing N=1485
No assessor at study site N=251
N=2904
Excluded:
Died in ICU <8d N=63
N=2841
Discharged alive from ICU <D8
N=2047
Still in ICU at D8
N=794
Random sample
N=261
Excluded:
NMD N=14
Denied N=1
Patient/assessor unavailble N=158
Excluded:
NMD N=36
Denied N=2
Patient/assessor unavailable N=108
Decrement N=6
Evaluated on the ward N= 88
Evaluated in ICU N= 642
With MRC
N= 72
Without MRC
N= 16
With MRC
N= 360
Without MRC
N= 282

Figure 3


Cumulative survival
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0,9
0,8
0,7
0,6
0,5
0,4
0,3
0
0
50
100
150
200
250
300
350
days
normal CMAP & no weakness
abnl CMAP & no weakness
normal CMAP & weakness
abnormal CMAP & weakness

Predictive value for weakness and 1-year mortality of screening electrophysiology tests in the ICU

Greet Hermans*, Helena Van Mechelen*, Frans Bruyninckx, Tine Vanhullebusch, Beatrix Clerckx, Philippe Meersseman, Yves Debaveye, Michael Paul Casaer, Alexander Wilmer, Pieter Jozef Wouters, Ilse Vanhorebeek, Rik Gosselink, Greet Van den Berghe.

*Equally contributed

Online Supplement

Methods

Patients

All patients with known neuromuscular disorders identified prior to ICU admission, or in whom a primary neuromuscular disorder was the reason for admission to the ICU were excluded. Among these were patients with diabetic polyneuropathy, alcoholic polyneuropathy, other polyneuropathies, steroid induced and other myopathies, spinal cord injury, central causes of neuromuscular dysfunction, Guillain Barré syndrome, myasthenia gravis, paraneoplastic neuromuscular disease, degenerative neuromuscular disorders, congenital disorders.

Electrophysiology

For the nerve conduction studies, 1 standard motor and 1 sensory nerve were evaluated in both upper and lower limbs unilaterally. If not evaluable, the contralateral side was used, or else the alternative nerve. For the motor nerves, we standardly used the tibial and median nerves, or alternatively the peroneal and ulnar nerves. The standard sensory nerves included the median and sural nerves, or alternatively the radial nerve. We used reference values generated in the KU Leuven electrophysiology laboratory (Table E1) and defined reduced CMAP and SNAP when below the lower limit of normal in both nerves of both limbs [19]. Repetitive stimulation of the median nerve at 3 Hz was performed to evaluate the neuromuscular junction, and if abnormal, the data of that specific electrophysiological test were excluded from analyses. Needle electromyography in rest was performed unilaterally in 1 standard proximal and 1 distal muscle in both upper and lower limbs. If not evaluable, the contralateral muscle was evaluated or else the alternative muscle. Standard muscles included extensor digitorum communis, biceps brachii, gastrocnemius and vastus lateralis of the quadriceps femoris. The alternative muscles included interosseus dorsalis I, pars media of the deltoid muscle, anterior tibial muscle, vastus medialis of the quadriceps femoris or rectus femoris. Abundant SEA was defined as the presence of

sustained fibrillation potentials and/or positive sharp waves after initial insertional activity in at least 2 muscles of at least 2 limbs.

MRC sum-score

MRC sum-score was evaluated as previously described (1). Briefly, cooperation of the patient was evaluated first using 5 standardized questions(1). Only when patients responded correctly to all of these, MRC sum-score was determined. Peripheral muscle strength was evaluated manually in a proximal, mid and distal muscle group of each upper and lower limb. This included abduction of the arm, flexion of the forearm, extension of the wrist, flexion of the hip, extension of the knee and dorsal flexion of the foot. All muscle groups were scored between 0 (no visible/palpable contraction) and 5 (normal muscle strength) and values were summed to obtain an MRC sum-score between 0 and 60. Manual muscle testing was performed by one of 2 physiotherapists extensively trained prior to the study, with good inter-observer reliability (2). The observers were blinded for results of electrophysiological testing. For each patient, we recorded first MRC sum-score determined as the first measurement made from day 8 onwards, the time-point that screening for awakening started for every patient. ICUAW was diagnosed if MRC sum-score was less than 48 (1).

Figure legends

Figure E1, panel A: Flow diagram CMAP

Flow diagram providing information on patients undergoing screening electrophysiological testing with CMAP as the test under evaluation (index test) and the MRC sum score as a reference test. Weakness was diagnosed when MRC sum score < 48.

CMAP: compound muscle action potential, MRC: Medical Research Council

Figure E1, panel B: Flow diagram SNAP

Flow diagram providing information on patients undergoing screening electrophysiological testing with SNAP as the test under evaluation (index test) and the MRC sum score as a reference test. Weakness was diagnosed when MRC sum score < 48.

SNAP: sensory nerve action potential, MRC: Medical Research Council

Figure E1, panel C: Flow diagram SEA

Flow diagram providing information on patients undergoing screening electrophysiological testing with SEA as the test under evaluation (index test) and the MRC sum score as a reference test. Weakness was diagnosed when MRC sum score < 48.

SEA: spontaneous electrical activity, MRC: Medical Research Council

Figure E2:

Receiver operating characteristics for the multivariate regression model on 1-year mortality.

The curve was constructed by use of predicted probabilities as the test variable and 1 year mortality as the state variable. The area under the curve is 0.779 (95%CI: 0.730-0.829)

Table E1: Reference values generated in the KU Leuven electrophysiology laboratory, stimulation and recording sites for CMAP and SNAP

		Cut-off	Location of stimulation	Location of recording
CMAP	Median nerve	< 6000 µV	Middle anterior wrist and elbow fold	M abductor pollicis brevis
	Ulnar nerve	< 4500 µV	Ulnar anterior wrist and medial epicondyle	M abductor digiti minimi
	Peroneal nerve	< 1000 µV	Anterior ankle and fibular head	M extensor digitorum brevis
	Tibial nerve	< 2500 µV	Inner ankle and knee fold	M flexor hallucis brevis
SNAP	Median nerve	< 4 µV	Middle anterior wrist	Palmar index finger
	Radial nerve	< 4 µV	Lateral edge of radius bone	Web space between digits I & II
	Sural nerve	< 4 µV	Lateral of Achilles tendon	At lateral malleolus

CMAP: compound muscle action potential, SNAP: sensory nerve action potential
SNAPs were measured antidromically with 14 cm distance between stimulation and recording site

Table E2: Univariate regression analysis of risk factors for 1-year mortality in the total EPaNIC population

	1y non-survivor N=743	1y survivor N=3884	P value
Baseline characteristic			
Randomization (early PN), N (%)	360/743 (48.5)	1944/3884 (50.1)	0.424
Age, median (IQR)	70 (60-78)	66 (55-74)	**<0.001**
Gender, male, N (%)	475/743 (63.9)	2485/3884 (64.0)	0.979
BMI 25-40, yes, N (%)	348/743 (46.8)	2193/3884 (56.5)	**<0.001**
NRS >=5, yes, N (%)	272/743 (36.6)	588/3884 (15.1)	**<0.001**
APACHE II, median (IQR)	32 (22-39)	18 (14-29)	**<0.001**
Diagnostic categories			**<0.001**
Emergent surgery, N (%)	283/743 (38.1)	881/3884 (22.7)	
Elective surgery, N (%)	64/743 (8.6)	213/3884 (5.5)	
Cardiac surgery, N (%)	224/743 (30.1)	2588/3884 (66.6)	
MICU	172/743 (23.1)	202/3884 (5.2)	
Diabetes, yes, N (%)	167/743 (22.5)	640/3884 (16.5)	**<0.001**
Malignancy, yes, N (%)	259/743 (34.9)	633/3884 (16.3)	**<0.001**
Dialysis pre-admission, yes, N (%)	23/743 (3.1)	46/3884 (1.2)	**<0.001**
Sepsis on admission, yes, N (%)	347/743 (46.7)	666/3884 (17.1)	**<0.001**
ICU risk factors up to day 8			
New infection, yes, N (%)	242/743 (32.6)	604/3884 (15.6)	**<0.001**
NMBA, yes, N (%)	249/743 (33.5)	488/3884 (12.6)	**<0.001**
Corticosteroids, days, median (IQR)	0 (0-4)	0 (0-0)	**<0.001**
Mechanical ventilation, days, median (IQR)	5 (2-8)	2 (1-3)	**<0.001**
Site of electrophysiological screening			
EMG&NCS performed on ICU, N (%)	217/230 (94.3)	423/498 (84.9)	**<0.001**

Abbreviations: PN: parenteral nutrition; BMI: Body Mass Index; NRS: Nutritional Risk Score; APACHE II: Acute Physiology And Chronic Health Evaluation II; MICU: medical intensive care unit; ICU: intensive care unit; NMBA: Neuromuscular Blocking Agents; EMG&NCS: Electromyography and Nerve Conduction Studies. Site of electrophysiological screening refers to testing in ICU or on the ward.
Survival status at 1 year was not available in 13 foreigners

Table E3. Baseline and outcome characteristic for patients who received electrophysiological screening according to length of stay

	Random sample short-stayer patients evaluated on the ward N=88	Long-stay patients evaluated in ICU N= 642
Baseline characteristics		
Age, years, median (IQR)	64 (53-75)	64 (53-74)
APACHE II score, median (IQR)	24 (16-33)	33 (26-39)
Sex, male sex, N (%)	47 (53.4)	415 (64.6)
BMI<25 or>40, N (%)	46 (52.3)	325 (50.6)
NRS <5, N (%)	69 (78.4)	437 (68.1)
Diabetes mellitus, N (%)	18 (20.5)	109 (17)
Malignancy, N (%)	21 (23.9)	162 (25.2)
Pre-admission dialysis, N (%)	1 (1.1)	11 (1.7)
Sepsis, N (%)	16 (18.2)	339 (52.8)
Admission category Cardiac surgery, N (%) Elective surgery, N (%) Emergent surgery, N (%) MICU, N (%)	 31 (35.2) 8 (9.1) 39 (44.3) 10 (11.4)	 172 (26.8) 21 (3.3) 309 (48.1) 140 (21.8)
Randomization to late PN, N (%)	48 (54.5)	315 (49.1)
Outcomes		
Duration MV, days, median (IQR)	2 (1-3)	11 (6-19)
Time to live weaning from MV, days, median (IQR)	2 (1-3)	12 (7-30)
ICU length of stay, days, median (IQR)	3 (2-4)	16 (11-26)
Time to live ICU discharge, days, median (IQR)	3 (2-4)	18 (11-40)
ICU mortality (N, %)	0 (0)	103 (16.0)
Hospital length of stay, days, median (IQR)[a]	16 (12-26)	35 (23-58)
Time to live hospital discharge, days, median (IQR)	16 (12-28)	54 (29-380)
Hospital mortality (N, %)	4 (4.5)	172 (26.8)
1y mortality (N, %)[b]	13 (14.8)	217 (33.9)
ICUAW (N, %)	3/72 (4.2)	201/360 (55.8)
CMAP abnormal, (N, %)	45/85 (52.9)	482/613 (78.6)

Abbreviations: MRC: Medical Research Council; IQR: interquartile range; APACHE II: acute physiology and chronic health evaluation; BMI: body mass index; NRS: nutritional risk score; MICU: medical ICU; ICU: intensive care unit; MV: mechanical ventilation; PN: parenteral nutrition; ICUAW: intensive care unit acquired weakness; CMAP: compound muscle action potential

Table E4. Univariate regression analysis of electrophysiological screening examination on day 8 and ICUAW for 1-year mortality

	Total population N=730			With MRC sum-score N=432			Without MRC sum-score N=298		
	1y non-survivor N= 230	1y survivor N= 498	P value	1y non-survivor N=95	1y survivor N=336	P value	1y non-survivor N=135	1y survivor N=162	P value
Electrophysiological data									
abnormal CMAP, N (%)	187/213 (87.8)	339/484 (70.0)	**<0.001**	79/88 (89.8)	223/327 (68.2)	**<0.001**	108/125 (86.4)	116/157 (73.9)	**0.010**
abnormal SNAP, N (%)	26/188 (13.8)	45/449 (10.0)	0.164	11/80 (13.8)	26/304 (8.6)	0.161	19/145 (13.1)	15/108 (13.9)	0.856
SEA present, N (%)	52/226 (23.0)	94/488 (19.3)	0.248	17/93 (18.3)	48/329 (14.6)	0.384	35/133 (26.3)	46/159 (28.9)	0.619
Clinical neuromuscular evaluation									
ICUAW, yes, N (%)	62/95 (65.3)	141/336 (42.0)	**<0.001**	62/95 (65.3)	141/336 (42.0)	**<0.001**	-	-	-

CMAP: Compound Muscle Action Potential; SEA: Spontaneous Electrical Activity; SNAP: Sensory Nerve Action Potential; ICUAW: Intensive Care Unit-Acquired Weakness

1-y survival status is unknown in 2 foreigners

Varying denominators are due to technical limitations precluding certain electrophysiological tests in some patients

Table E5. Outcomes according to results of CMAP on electrophysiological screening performed on day 8±1 after ICU admission

	Total population			**With MRC**			**Without MRC**		
	Abnormal CMAP N=527	**Normal CMAP N=171**	**p-value**	**Abnormal CMAP N=302**	**Normal CMAP N=113**	**p-value**	**Abnormal CMAP N=225**	**Normal CMAP N=58**	**p-value**
First MRC sum-score, median (IQR)	46 (38-52)	53 (48-58)	**<0.001**	46 (38-52)	53 (48-58)	**<0.001**	-	-	-
First MRC sum-score <48, N (%)	171 (56.6)	22 (19.5)	**<0.001**	171 (56.6)	22 (19.5)	**<.0001**	-	-	-
Duration MV, days, median (IQR)	10 (6-19)	7 (2-12)	**<0.001**	9 (5-19)	5 (2-11)	**<0.001**	11 (6-19)	9 (5-15)	0.189
Time-to-live weaning from MV, days, median (IQR)	11 (6-27)	7 (2-13)	**<0.001**	9 (5-20)	5 (2-11)	**<0.001**	14 (7-283)	10 (5-20)	**0.039**
ICU length of stay, days, median (IQR)	15 (10-25)	12 (8-18)	**<0.001**	15 (10-28)	10 (4-18)	**<0.001**	14 (10-22)	13 (9-21)	0.449
Time-to-live ICU discharge, days, median (IQR)	17 (10-38)	12 (8-19)	**<0.001**	16 (10-29)	10 (4-18)	**<0.001**	18 (11-283)	14 (10-27)	**0.078**
ICU mortality, N (%)	79 (15.0)	13 (7.6)	**0.013**	16 (5.3)	2 (1.8)	0.126	63 (28.0)	11 (19.0)	0.163
Hospital length of stay, days, median (IQR)	35 (22-61)	27 (15-42)	**<0.001**	39 (25-66)	26 (14-41)	**<0.001**	31 (20-51)	28 (21-43)	0.388
Time-to-live hospital discharge, days, median (IQR)	54 (28-380)	29 (17-50)	**<0.001**	46 (27-96)	27 (14-43)	**<0.001**	94 (33-380)	39 (23-380)	**0.001**
Hospital mortality, N (%)	142 (26.9)	19 (11.1)	**<0.001**	45 (14.9)	4 (3.5)	**0.001**	97 (43.1)	15 (25.9)	**0.017**
1-y mortality, N (%)	187 (35.6)	26 (15.2)	**<0.001**	79 (26.2)	9 (8.0)	**<0.001**	108 (48.2)	17 (29.3)	**0.010**

CMAP: Compound Muscle Action Potential; MRC: Medical Research Council; MV: mechanical ventilation; IQR: interquartile range

Figure E1, panel A

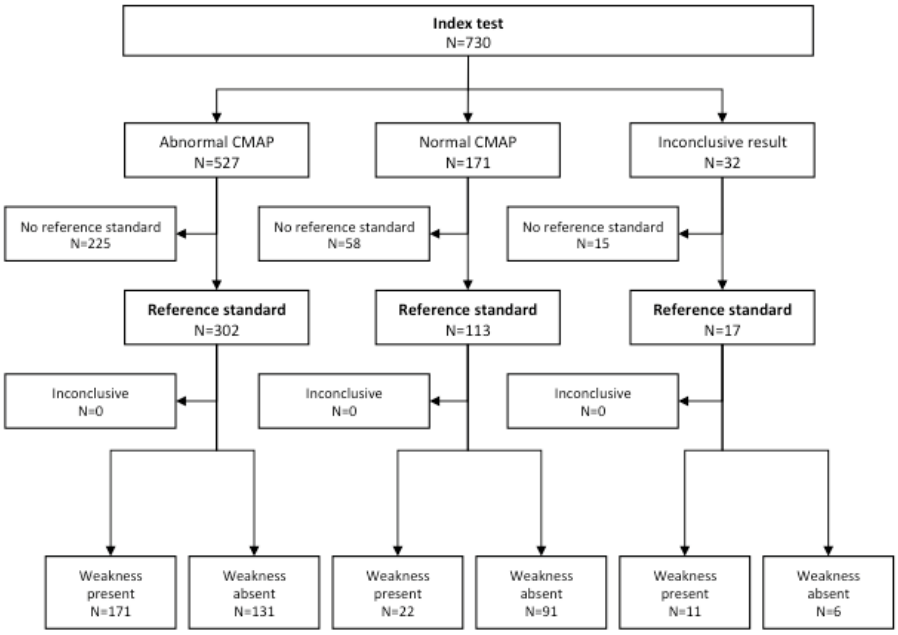


Figure E1, panel B

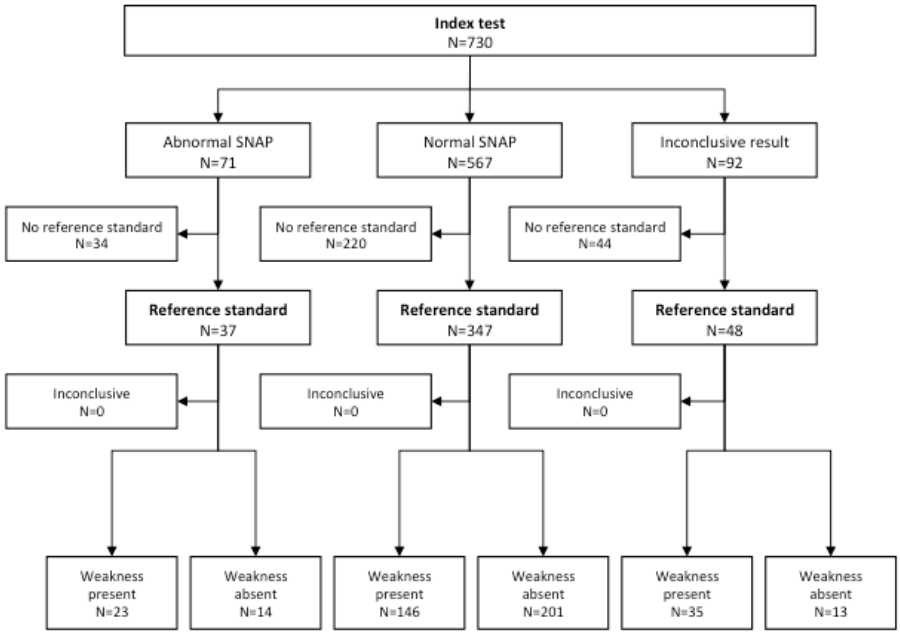


Figure E1, panel C

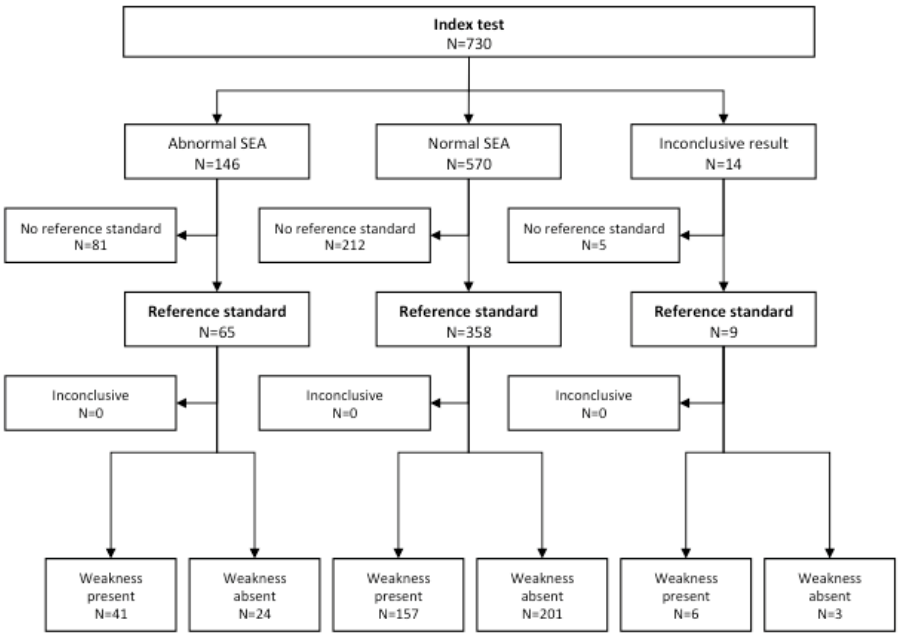
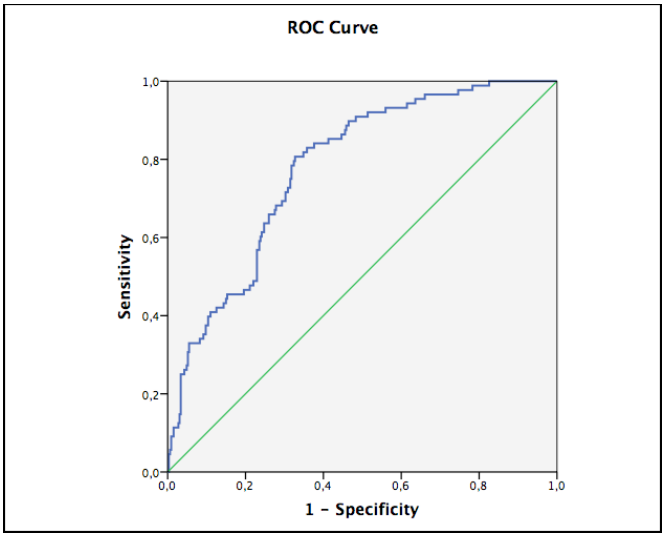


Figure E2:



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